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Arsenic Concentrations in Prediagnostic Toenails and the Risk of Bladder Cancer in a Cohort Study of Male Smokers

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At high concentrations, inorganic arsenic can cause bladder cancer in humans. However, it is unclear whether low exposure to inorganic arsenic in drinking water (<100 μg/liter) is related to bladder cancer risk. No study has been known to use biomarkers to assess the relation between individual arsenic exposure and bladder cancer risk. Toenail samples provide an integrated measure of internal arsenic exposure and reflect long-term exposure. The authors examined the relation between toenail arsenic levels and bladder cancer risk among participants in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a cohort of Finnish male smokers aged 50–69 years. Data for 280 incident bladder cancer cases, identified between baseline (1985–1988) and April 1999, were available for analysis. One control was matched to each case on the basis of age, toenail collection date, intervention group, and smoking duration. Arsenic levels in toenail samples were determined by using neutron activation analysis. Logistic regression analyses were performed to estimate odds ratios. Arsenic toenail concentrations in this Finnish study were similar to those reported in US studies (range: 0.02–17.5 μg/g). The authors observed no association between inorganic arsenic concentration and bladder cancer risk (odds ratio = 1.13, 95% confidence interval: 0.70, 1.81 for the highest vs. lowest quartile). These findings suggest that low-level arsenic exposure is unlikely to explain a substantial excess risk of bladder cancer.

arsenic; bladder neoplasms; cohort studies; nails; smoking

Abbreviation: ATBC, Alpha-Tocopherol, Beta-Carotene.

Ecologic studies in regions of Taiwan, Argentina, and Chile, where artesian wells contain high concentrations of inorganic arsenic (>150 μg/liter), have consistently reported elevated bladder cancer incidence and mortality rates compared with low-exposure populations (1–7). In two cohort studies conducted in parts of Taiwan with endemic arsenic levels in drinking water, an elevated bladder cancer incidence was observed among those with the highest arsenic levels (8, 9). Elevated bladder cancer mortality rates have also been observed among people exposed to high levels of arsenic from industrial contamination (10) or from Fowler's solution, which contains 1 percent potassium arsenite (11). Given the evidence linking inorganic arsenic in drinking water to bladder cancer, the National Research Council recently concluded that ingestion of arsenic in drinking water causes bladder cancer (12, 13).

Despite the known relation between high inorganic arsenic exposure and bladder cancer, few studies have been able to address whether low-level arsenic exposure increases the risk of bladder cancer. No overall association was reported between arsenic levels in drinking water (range: 10–50 μg/liter) and bladder cancer risk in a US case-control study, although a slight elevation in risk was observed for the highest arsenic exposure among male smokers aged 30–39 years before the interview (14). In contrast, a recent Finnish case-cohort study reported a greater than twofold increase in bladder cancer risk with low-level arsenic exposure from drinking water (2–9 years before diagnosis) (15). In a cohort

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study in Taiwan, relative risks of 1.5 (95 percent confidence interval: 0.3, 8.0) and 2.2 (95 percent confidence interval: 0.4, 13.7) were observed for bladder cancer among those with well-water arsenic concentrations of 10.1–50 μg/liter and 50.1–100 μg/liter, respectively, compared with <10 μg/liter (in an arseniasis-endemic area) (8). A recent case-control study conducted in the United States reported no elevation in bladder cancer risk at low levels of arsenic exposure in drinking water (<80 μg/liter) (16). Extrapolations from studies of high arsenic exposure suggest that levels as low as 20–50 μg/liter may increase the risk of bladder cancer (12, 13). However, risk estimates depend on 1) assumptions made, 2) modeling used, and 3) comparison population choices, and changing these can result in a wide range of estimates (17).

No study has been known to use biomarkers to evaluate the relation between internal levels of arsenic and bladder cancer risk. Because toenails grow slowly (0.75 mm/month) (18), trace-element measurements from toenail clippings reflect internal exposure 9–18 months prior to collection, depending on the length of the toenail. Studies have shown that arsenic levels measured in toenails remain relatively constant over spans of up to 6 years (19, 20), which suggests that arsenic measurements obtained from a single toenail sample reflect long-term exposure. Toenails provide an integrated measure of internal inorganic arsenic exposure and reflect all sources of exposure, including drinking water, diet, and occupation.

To better estimate the relation between low-level arsenic exposure and bladder cancer risk, we conducted a nested case-control study in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study. For this study, arsenic concentrations in prediagnostic toenail samples were successfully measured in 280 bladder cancer cases and 293 controls matched on age, toenail collection date, smoking duration, and trial intervention group.

MATERIALS AND METHODS

Study population

The ATBC Study was initiated between 1985 and 1988 when 29,133 male smokers, aged 50–69 years and living in southwestern Finland, were recruited to participate in a prevention trial. The study was a randomized, double-blinded, placebo-controlled trial designed to test the effect of alpha-tocopherol (50 mg/day) and beta-carotene (20 mg/day) supplementation on lung cancer incidence by using a 2×2 factorial design. Although the trial ended in 1993, data on cancer endpoints have been routinely updated. At baseline, men were excluded from the trial if they smoked fewer than five cigarettes per day, had prior cancer, had a serious disease limiting long-term participation, or were users of vitamins E or A or beta-carotene supplements in excess of predefined doses. The rationale, methods, participation characteristics, compliance, and main results of the ATBC Study are described in detail elsewhere (21, 22). The study was approved by the institutional review boards of both the National Public Health Institute in Finland and the National Cancer Institute in the United States.

All participants provided toenail clippings (from all 10 toes) upon entry into the trial (1985–1988). In addition, data on health status, smoking, height, weight, and other characteristics were obtained at the time of entry into the trial.

For this analysis, one control was matched to every bladder cancer case on the basis of age (within a 2-year interval), date of toenail collection (within 1 month), intervention group, and smoking duration (≤35 or >35 years).

Follow-up of cancer incidence

From baseline to April 1999, all cases of bladder cancer were identified through the Finnish Cancer Registry, through the Hospital Discharge Registry, and from death certificates, providing close to complete case ascertainment. For bladder cancer, case ascertainment has been found to be 95 percent complete within 0.8 years when using data from the Finnish Cancer Registry alone; case ascertainment increases when cases obtained from the Hospital Discharge Registry and death certificates are included (23). Only histologically confirmed cases of incident bladder cancer were included in the present analysis (*International Classification of Diseases*, Ninth Revision, codes 188 and 233.7) (24); cancers of the renal pelvis, ureter, and urethra (*International Classification of Diseases*, Ninth Revision, codes 189.1, 189.2, and 189.3) (24) were not included. Data for 331 bladder cancer cases with baseline toenail clippings were available for arsenic determination. The time lag from toenail collection to cancer diagnosis was 1–14 years.

Determination of toenail arsenic concentration

Both intact toenails (191 cases, 305 controls) and pulverized toenails (140 cases, 26 controls) were used for this analysis. To remove external surface contamination, intact toenails were first sent to National Cancer Institute–Frederick laboratories in Maryland to be cleaned. Pulverized toenails (from a previous study) were not cleaned. Arsenic levels were determined by using neutron activation analysis at North Carolina State University's Department of Nuclear Engineering. The samples were divided into five batches and were irradiated for 14 hours each in the PULSTAR nuclear research reactor (in rotating exposure ports) at a power of 900 kW of thermal energy. Each batch of samples was left to decay for 5–6 days (to allow sodium-24 to decay and to improve the signal-to-noise ratio for the As-76 signature; the amount of decay time prior to counting is determined almost exclusively by the sodium content of the sample (25)). Samples were subsequently counted for 10–30 minutes each by using a gamma spectroscopy system analyzing for arsenic. Because of possible contaminants in the toenail samples, arsenic concentrations were not always detectable in the samples available, and the arsenic detection limit varied across the samples. To avoid misclassification of samples with high detection limits, we excluded those with nondetectable arsenic levels whose detection limits were greater than 0.09 μg/g (51 cases and 38 controls). The cutpoint (0.09 μg/g) was based on the highest arsenic value of the lowest quartile when all samples with nondetectable

values were excluded. For 59 cases and 69 controls who also had nondetectable values but had detection limits equal to or less than 0.09 μg/g, we assigned an arsenic value equal to the detection limit divided by 2. The final sample size was 280 cases and 293 controls.

Blanks, quality assurance controls, and arsenic standards were included in each of the five irradiation batches. Reference material for quality assurance included dogfish muscle and liver, supplied and certified by the National Research Council Canada, and tuna, supplied and certified by the US National Institute of Standards and Technology. In addition, three toenail samples were split in half (because of a large volume) and were measured separately. When the reference material was used, the coefficient of variation percentage was 6.98 overall. For the three duplicate toenail samples, the coefficient of variation percentage was 1.13.

Dietary assessment

At baseline, participants were asked to complete a food-use questionnaire that included 276 food and beverage items commonly consumed in Finland. A color picture book was provided to guide the subjects with respect to portion sizes. Participants were asked to report their average intake and portion size for each food over the previous 12 months. We estimated total beverage intake by summing over all beverages on the questionnaire. However, because plain water intake was not among the questions asked, the "total" beverage variable does not include water consumption.

Statistical analysis

Odds ratios and 95 percent confidence intervals were estimated by using unconditional logistic regression models to adjust for matching factors, number of cigarettes smoked per day (continuous), and smoking duration (years; continuous). Other factors, such as smoking cessation, smoking inhalation, educational level, beverage intake, and place of residence, were also considered as potential confounders. Results using conditional regression models were similar to those using the unconditional models (no effect of arsenic); however, since the numbers were smaller because of exclusions made for nondetectable arsenic measurements, we present only unconditional models in this paper. Men were categorized into quartiles based on the distribution of arsenic among the controls. Tests for trend were conducted by using the median value for each quartile and modeling it as a continuous variable. Effect modification by smoking characteristics, place of residency, beverage intake, and toenail weight was evaluated in stratified analyses and by adding the relevant cross-product term to main-effects models. To preserve power, arsenic levels were divided into tertiles in all stratified analyses. *P* values for case-control differences were calculated by using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables.

RESULTS

Baseline characteristics of participants in this nested case-control study, including smoking dose, smoking cessation,

TABLE 1. Baseline characteristics of bladder cancer cases and controls* in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Finland, 1985–1999

	Cases (*n* = 280)	Controls (*n* = 293)
Arsenic level in μg/g (median (range))	0.110 (0.014–2.62)	0.105 (0.017–17.5)
Age in years (mean (SD†))	59.4 (5.1)	59.5 (5.0)
Smoking history (mean (SD))		
No. of years of smoking regularly	39.8 (7.4)	39.1 (8.0)
No. of cigarettes/day	20.2 (7.8)	19.5 (7.8)
Smoking inhalation (%)		
Never/seldom	6.1	5.8
Often/always	93.9	94.2
Smoking cessation (%)	15.4	16.0
Urban residence (%)	45.4	38.9
Educational level (%)		
Primary school	67.5	70.0
High school	7.5	5.5
Vocational	20.4	20.8
University	4.6	3.7
Total beverage intake in ml/day‡ (mean SD))	1,534 (471)	1,569 (523)

* None of the case-control differences was statistically significant at the 0.05 level.
† SD, standard deviation.
‡ Based on 262 cases and 275 controls for whom dietary information was complete. Total beverage intake was adjusted for energy and includes coffee, tea, milk, juice, soft drinks, beer, wine, and liquor.

TABLE 2. Multivariate odds ratios and 95% confidence intervals for bladder cancer according to quartiles and percentiles of toenail arsenic level in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study,* Finland, 1985–1999

	Median arsenic level (μg/g)*	Cases (no.)	Controls (no.)	OR†	95% CI‡
Quartile (range in μg/g)*					
1 (<0.050)	0.033	65	74	1.0	
2 (0.050–0.105)	0.079	71	73	1.09	0.68, 1.74
3 (0.106–0.161)	0.130	73	73	1.13	0.71, 1.80
4 (>0.161)	0.245	71	73	1.13	0.70, 1.81
p trend				0.65	
Percentile (range in μg/g)*					
≤50 (<0.105)	0.050	136	147	1.0	
50.1–75 (0.105–0.160)	0.130	73	72	1.10	0.73, 1.64
75.1–90 (0.161–0.259)	0.198	37	44	0.93	0.56, 1.54
90.1–95 (0.260–0.399)	0.333	20	16	1.38	0.68, 2.80
95.1–100 (>0.399)	0.757	14	14	1.14	0.52, 2.51
p trend				0.61	

* In controls.

† Odds ratios (OR) were estimated from unconditional logistic regression models adjusted for matching factors (age, date at toenail collection, and intervention group), no. of cigarettes/day (continuous), and no. of years of smoking (continuous).

‡ CI, confidence interval.

educational level, urban residence, and beverage intake, were similar for bladder cancer cases and controls (table 1). The median arsenic concentration among controls was 0.105 μg/g (or ppm), and the concentration ranged from 0.02 μg/g to 2.11 μg/g (with one outlier at 17.5 μg/g).

Arsenic levels were not associated with the risk of bladder cancer, even for those whose toenail arsenic concentrations were above the 95th percentile compared with concentrations at or below the median (table 2). When we controlled for other potential confounders, including education, place of residence, smoking inhalation and cessation, and beverage intake, the risk estimates did not change. Similar findings were observed in a lag analysis in which data on cases from the first 5 years of follow-up were removed (data not shown). Furthermore, removing all toenail samples with nondetectable arsenic concentrations did not change the associations displayed in table 2 (data not shown).

Because the previously pulverized toenail samples were not cleaned prior to the arsenic measurements, potential external contamination could have introduced measurement error. To explore this possibility, we removed data on the pulverized toenails from the analysis. Results were similar among the whole toenails (data not shown). In addition, because low sample weight may reduce accuracy of the arsenic determination, we stratified by sample weight; results in both strata were similar to the overall findings (table 3).

For those men who had smoked cigarettes for more than 45 years, the highest tertile of arsenic level was associated with a twofold increase in the risk of bladder cancer; however, this association was statistically nonsignificant, and no association with arsenic was observed for men who smoked 30 or more cigarettes per day (table 3). No statistically significant effect modification was observed for smoking dose, number of years of smoking, place of residence, or beverage intake (table 3). Furthermore, for men living in rural areas, the slightly elevated risk observed in the highest tertile of arsenic level was not observed when quartiles instead of tertiles were used for the same stratified analysis (data not shown).

DISCUSSION

In this nested case-control study of male smokers, we observed no elevation in bladder cancer risk for men with the highest toenail arsenic concentrations compared with those with the lowest. Restricting analyses to the heavier toenail samples or to samples with detectable levels of arsenic yielded similar findings. Smoking dose, smoking duration, or place of residence did not modify the association.

The US Environmental Protection Agency has used risk assessment models to estimate the maximum contamination level in drinking water, a level below which no known adverse health effects occur. For arsenic and bladder cancer, this agency has relied heavily on data from Taiwan. These risk assessment models make assumptions about dose-response curves because low-dose exposure data are not available or are not reliable. When these models are used, the relative risk of bladder cancer for being exposed to arsenic levels of 50 μg/liter in drinking water has been estimated to be about 1.2–2.5 (13). However, there are many limitations to using data from Taiwan, including differences in the environment, diet, and genetic susceptibility. In the absence of internal exposure data, the dose-response relation between

TABLE 3. Multivariate odds ratios and 95% confidence intervals for bladder cancer according to tertile of toenail arsenic level, stratified by selected factors, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Finland, 1985–1999

	Tertile of arsenic (μg/g)								*p* for trend
	0.017–0.070		0.071–0.137			>0.137			
	Cases (no.)	OR*	Cases (no.)	OR*	95% CI†	Cases (no.)	OR*	95% CI	
No. of years of smoking									
≤35	16	1.0	21	1.14	0.45, 2.93	30	1.30	0.55, 3.06	0.56
36–45	57	1.0	50	0.90	0.53, 1.53	60	1.16	0.69, 1.95	0.53
>45	11	1.0	18	1.46	0.52, 4.13	17	2.30	0.77, 6.88	0.14
No. of cigarettes/day									
<20	29	1.0	32	1.01	0.51, 2.00	35	1.09	0.55, 2.17	0.79
20–29	38	1.0	39	1.02	0.55, 1.89	62	1.99	1.09, 3.64	0.02
≥30	17	1.0	18	2.48	0.79, 7.75	10	0.65	0.20, 2.08	0.44
Total beverage intake (ml/day)‡									
≤1,307	29	1.0	28	0.92	0.44, 1.92	36	1.57	0.75, 3.27	0.21
1,308–1,720	31	1.0	25	0.66	0.31, 1.40	32	1.21	0.58, 2.53	0.54
>1,720	23	1.0	32	1.44	0.66, 3.14	26	0.76	0.35, 1.65	0.36
Place of residence (population)									
Rural (<50,000)	40	1.0	54	1.15	0.67, 1.98	59	1.59	0.91, 2.78	0.09
Urban (≥50,000)	44	1.0	35	1.02	0.53, 1.98	48	1.00	0.55, 1.83	0.99
Toenail weight (g)									
Small (≤0.141)	45	1.0	38	0.67	0.37, 1.23	73	1.24	0.71, 2.17	0.26
Large (>0.141)	39	1.0	51	1.47	0.82, 2.62	34	0.97	0.51, 1.85	0.92

* Odds ratios (ORs) were estimated from unconditional logistic regression models adjusted for matching factors (age, date at toenail collection, and intervention group), no. of cigarettes/day (continuous), and no. of years of smoking (continuous).

† CI, confidence interval.

‡ Based on 262 cases and 275 controls for whom dietary information was complete. Total beverage intake was adjusted for energy and includes coffee, tea, milk, juice, soft drinks, beer, wine, and liquor.

low arsenic exposure and bladder cancer risk remains speculative.

Toenail arsenic levels in the ATBC Study population were comparable to those reported in previous US studies (ranges: 0.01–0.81 μg/g (26); 0.01–2.57 μg/g (27); mean, 0.12 (standard deviation, 0.27) μg/g (19)). In countries where arsenic levels in drinking water are not extremely high, other sources of inorganic arsenic, including dietary or occupational exposures, may be important contributors to total inorganic arsenic exposure. Toenail samples have been shown to provide a good biologic marker for quantifying low-level arsenic exposure, and they provide an integrated measure of all arsenic sources (28). A study on skin cancer conducted in New Hampshire reported a twofold increase in the risk of squamous cell carcinoma among those with toenail arsenic levels of 0.35–0.81 μg/g (26), which is within the levels observed in our study.

In a study validating toenails as biomarkers of arsenic ingestion from water, water arsenic levels ranged from 0.002 to 66.6 μg/liter and toenail arsenic levels ranged from less than 0.01 to 0.81 μg/g (28). The correlation between the two was 0.65 among persons whose arsenic levels were equal to or greater than 1 μg/liter (28). When the linear regression analysis from this validation study was used, the 50th, 75th, 90th, and 95th percentiles of toenail arsenic levels in the ATBC Study reflected water arsenic levels of roughly 2, 10, 50, and 100 μg/liter, respectively (28). In the United States, public water supplies are currently regulated by the Environmental Protection Agency to remain below 50 μg/liter (13), with a new standard maximum contamination level of 10 μg/liter to become effective in January 2006. Our results suggest that arsenic exposure levels of around 50 μg/liter do not increase the risk of bladder cancer. Given our small sample size in the top percentiles, we cannot exclude the possibility that exposure levels of about 100 μg/liter may be associated with bladder cancer risk. Similarly, we cannot exclude the possibility that subgroups who are highly susceptible (genetic or environmental) may be at higher risk at lower arsenic levels. For example, animal studies suggest that certain environmental factors, such as selenium, lead, or cadmium, may inhibit the second arsenic methylation step in arsenic metabolism (13).

The ATBC Study consists of male smokers; therefore, our findings may not be generalizable to women or to nonsmokers. However, in three studies with data on low arsenic exposure, elevated risks were observed for smokers only (14–16). In the Finnish study, a relative risk of 10 was observed for smokers exposed to more than or equal to 0.5

μg/liter compared with less than 0.1 μg/liter of arsenic in drinking water when exposure was assessed within 3–9 years prior to diagnosis, but no association was found for never smokers (15). Because prior studies suggest that smokers are more susceptible than nonsmokers to arsenic exposure, the ATBC Study provides a good population in which to examine the relation between low-level arsenic and bladder cancer risk.

Measurement error in the assessment of arsenic in toenails could have attenuated relative risks in this study. In a reproducibility study of arsenic toenail measurements over a 6-year period, the authors assessed the effect of random within-person variability on odds ratios (19). They demonstrated that, in a case-control study setting, a true odds ratio of 3.0 would be observed as 2.15 (for a comparison of the highest quintile vs. the remaining four quintiles of arsenic exposure), and, similarly, an odds ratio of 1.5 would be attenuated to 1.32 (19).

Although reproducibility of arsenic levels in toenails over several decades is unknown, random variability is likely to increase over time because of relocation and changes in drinking water sources. Movement of subjects in the ATBC cohort is unlikely to have caused substantial misclassification, however, because migration in this population of older men is likely to have been low. Statistics from Finland indicate that internal migration (within and between municipal regions, and between provinces) averaged 14 percent annually between 1961 and 2002 (29), and 80 percent of the relocations occurred among the younger age groups (35 years or less) (29). Nevertheless, given the potential for increasing misclassification of exposure over time, and with the knowledge that the latency period for bladder cancer is in excess of 20 years (13) and may be as long as 50 years for arsenic exposure (16, 30), we cannot rule out an association between low-dose arsenic exposure and bladder cancer among smokers.

In summary, we observed no association between low-level arsenic exposure and bladder cancer risk in a Finnish population followed up for as long as 14 years. This study is the first known to examine the association between internal inorganic arsenic exposure and bladder cancer risk using a biomarker. The present study suggests that arsenic exposure is unlikely to explain a substantial excess of bladder cancer in Finland or in countries with low arsenic exposure. Other, similar studies are needed to confirm these findings, especially for women.

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